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Comment

## Network meta-analysis: a new norm for comparing treatments

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In this issue, Siontis and colleagues compare an array of possible percutaneous coronary interventions (PCI) for treatment of in-stent restenosis.<sup>1</sup> Most readers will recognize the hallmarks of a typical systematic review, with pre-defined eligibility criteria, a thorough search for studies, assessments of risk of bias for each study, consideration of the possibility of publication bias, and statistical combination (meta-analysis) of results across studies. Perhaps the most interesting aspect of their methodology, however, is the authors' use of the increasingly popular technique of network meta-analysis. Network meta-analysis allows the authors to compare the effectiveness of each of eight treatments with any of the others, even when for some pairs of treatments there are no trials of head-to-head comparisons.

Network meta-analysis methods arose through some disconnected developments during the early 1990s,<sup>2-4</sup> and after a dormant period were revitalized about 10 years later.<sup>5</sup> Since then they have earned a critical role in comparative effectiveness research, particularly in organizations developing guidance and quality standards for health care, such as the National Institute for Health and Care Excellence (NICE) in the UK and the Canadian Agency for Drugs and Technologies in Health. The term 'network meta-analysis', apparently first used in 2002,<sup>6</sup> is inspired by a graph illustrating which treatments have been compared directly with each other within primary studies, as in Figure 1 of Siontis and colleagues.<sup>1</sup> Network meta-analyses can be used to compare all treatments that are connected to each other in this network plot. The term appears to have become the generally preferred term over earlier competitors such as 'multiple treatments meta-analysis' and 'mixed treatment comparisons'.

At the heart of the network meta-analysis method is the notion of an 'indirect comparison'. In the absence of a direct head-to-head comparison of two treatments, we must draw on results of separate studies involving those treatments. A naïve indirect comparison could be made by comparing outcomes of people receiving one treatment in one study with people receiving the other treatment in a different study. But this could easily give the wrong answer, since it fails to account for key differences between the studies and loses the advantages of randomizing patients in the first place: perhaps one study was longer than the other, or involved people with more severe disease. Instead we need to find points of reference across the two studies. This is provided by seeking studies that used a common comparator. Thus, for example, everolimus-eluting stents (EES) and balloon angioplasty (BA) have not been compared directly in a randomized trial, but both have been compared in separate trials with drug-coated balloons (DCB).<sup>1</sup> The indirect comparison builds on the argument that if patients do better on EES than on DCB, and if they do better on DCB than on BA, then they ought to do better on EES than on BA. A network meta-analysis formalizes this argument mathematically, thus defining connections between the trials making different comparisons of treatments. It combines the results from all studies simultaneously, drawing on both direct comparisons within studies and indirect comparisons across studies via common reference treatments.

A key strength of network meta-analysis is that it can lead to a single, coherent, ranking of the treatments. Among the percutaneous coronary interventions, clear winners from Siontis and colleagues were everolimus-eluting stents and drug-coated balloons. Across several clinical endpoints, these had high probabilities of being at the top of the ranking, and low probabilities of being low in the ranking. The authors were fortunate that the messages were clear. There was little between-study variation in their meta-analyses, and no evidence that the assumptions underlying the indirect comparisons were unreasonable.

Complications and considerations in network meta-analysis have been discussed in several accessible texts.<sup>7-12</sup> Differences between network meta-analysis and standard meta-analysis are not, in our view, as substantial as many fear. In a standard meta-analysis it is widely recognized that the studies need to be sufficiently similar to each other for the combined result to be meaningful. In a network meta-analysis, they need to be sufficiently similar in ways other than the particular choice of treatments being compared. This will not always be the case, but requires the same type of reasoning that ought to be used when making the decision to combine across studies in a standard meta-analysis.

Although there are additional technical challenges in network meta-analysis from a statistical perspective, which we won't go into here, there are also interesting opportunities to interrogate the evidence in new ways. For instance, if both a direct comparison and an indirect comparison is available for a pair of treatments, then we can examine whether they agree with each other. For example, Siontis and colleagues identified trials of each of DCB and BA against paclitaxel-eluting stents (PES).<sup>1</sup> Fortunately, the indirect comparison of DCB vs BA through the common comparator of PES did not conflict with the direct head-to-head trials of DCB vs BA. Furthermore, there was a three-arm trial of all three of these treatments that added further justification to the joint synthesis. Examinations like this are known as investigations of 'incoherence' or 'inconsistency' and will often be found in a report of a network meta-analysis. If incoherence is identified it may be due to various factors, including non-comparability of the studies or different biases affecting different comparisons.<sup>7</sup> Strategies for addressing incoherence include (i) narrowing the criteria for including studies in the analysis, (ii) exploring possible causes using meta-regression, and (iii) refraining from synthesizing the data.

One of the challenges in network meta-analyses is how to convey the complex set of outputs from the analysis. Results are available for all pair-wise comparisons of treatments in the network. With five treatments this produces 10 pairs; for 10 treatments we have 45 pairs; and for 20 treatments we have 190 pairs. With relatively small numbers of treatments, we can illustrate all pair-wise comparisons in matrices such as those Siontis and colleagues use for their eight treatments. For larger problems some reduction may be needed, such as restriction to the treatments of primary interest or grouping of similar treatments; there is undoubtedly room for development of novel presentational approaches. Caution is often required when networks appear to be large (in terms of number of treatments) but contain sparse data (just one or two studies for each available direct comparison).

It is not surprising that network meta-analyses have become so popular, given that they answer the real questions of interest to decision makers, who are usually faced with an array of treatment options and not just two. They are the natural evolution of meta-analysis, and they rest on fundamentally the same considerations as all other meta-analyses. We anticipate that they will become the new 'norm' for combining results of multiple clinical trials. They are not without challenges, but then neither are any other approaches to combining evidence across studies that were not designed with their statistical synthesis in mind. And unlike standard meta-analyses, network meta-analyses offer a valuable opportunity to examine whether a body of evidence is

coherent, by ‘triangulating’ across trials making different comparisons of treatments for the same condition.

## References

1. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for the treatment of in-stent restenosis: a network meta-analysis. *The Lancet* 2015.
2. Eddy DM, Hasselblad V, Shachter R. Meta-analysis by the Confidence Profile Method. San Diego: Academic Press; 1992.
3. Gleser LJ, Olkin I. Stochastically dependent effect sizes. In: Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. New York: Russell Sage Foundation; 1994: 339-56.
4. Higgins JPT, Whitehead A. Borrowing strength from external trials in a meta-analysis. *Statistics in Medicine* 1996; **15**: 2733-49.
5. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006; **101**(474): 447-59.
6. Lumley T. Network meta-analysis for indirect treatment comparisons. *Statistics in Medicine* 2002; **21**(16): 2313-24.
7. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Meth* 2012; **3**(2): 80-97.
8. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2011; **14**(4): 417-28.
9. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005; **331**(7521): 897-900.
10. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013; **159**(2): 130-7.
11. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ* 2013; **346**: f2914.
12. Dias S, Welton NJ, Sutton AJ, Ades AE, and others. Evidence synthesis for decision making (Series of 7 papers). *Medical Decision Making* 2013; **33**: 597-691.